OBSERVATIONAL STUDY ON PEGYLATED GROWTH FACTOR IN ACUTE MYELOID LEUKEMIA CONSOLIDATION

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Certificate

*This is to certify that the dissertation entitled "**ROLE OF PEGYLATED GOWTH FACTOR IN AML CONSOLIDATION"**is a bonafide work done by **Dr Prashanth Parameswar**, College of Oncological Sciences, Cancer Institute (W.I.A) in partial fulfilment of the university rules & regulations for award of D.M Medical Oncology under my guidance & supervision during the academic year 2011 – 2014.*

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A Word of Gratitude

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Certificate by ITRC

This is to certify that the dissertation entitled **"Observational study of Pegylated Growth factors in AML Consolidation phase of treatment"** has been approved by Institute Thesis Review Committee

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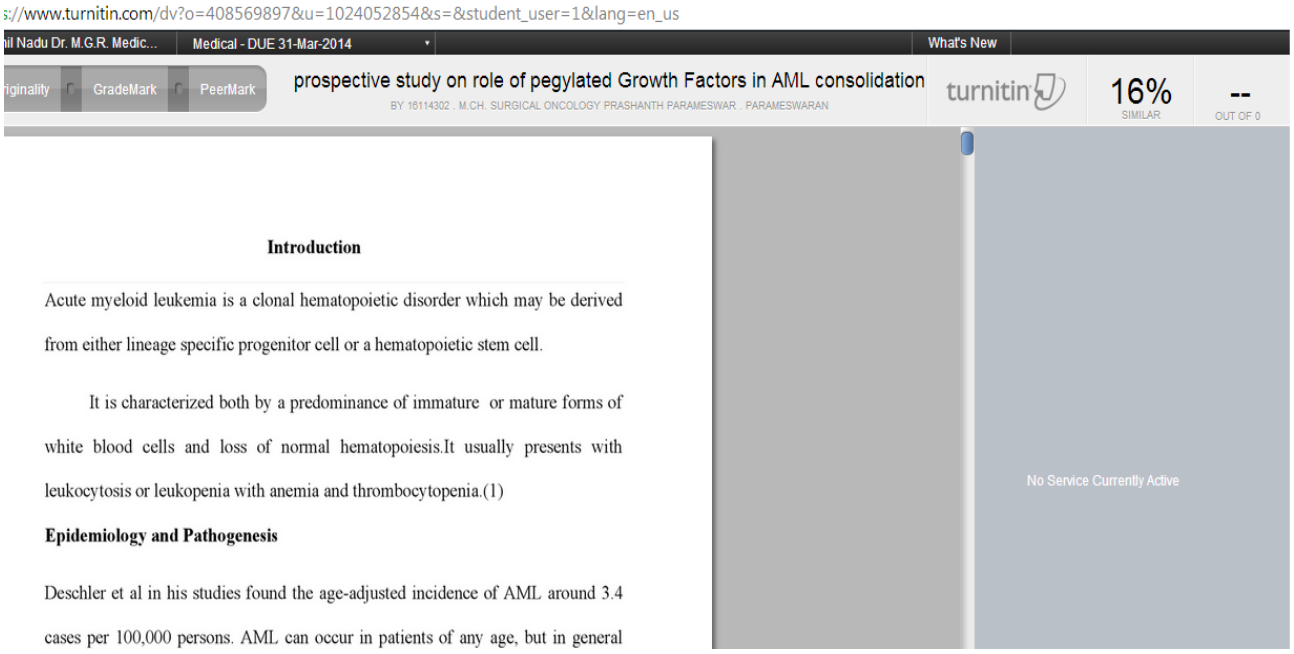
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Introduction
Acute myeloid leukemia is a clonal hematopoietic disorder which may be derived from either lineage specific progenitor cell or a hematopoietic stem cell.
It is characterized both by a predominance of immature or mature forms of white blood cells and loss of normal hematopoiesis.It usually presents with leukocytosis or leukopenia with anemia and thrombocytopenia.(1)
Epidemiology and Pathogenesis
Deschler et al in his studies found the age-adjusted incidence of AML around 3.4 cases per 100,000 persons. AML can occur in patients of any age, but in general
No Service Currently Active

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INTRODUCTION

Acute myeloid leukemia is a clonal hematopoietic disorder which may be derived from either lineage specific progenitor cell or a hematopoietic stem cell.

It is characterized both by a predominance of immature or mature forms of white blood cells and loss of normal hematopoiesis. It usually presents with leukocytosis or leukopenia with anemia and thrombocytopenia.(1)

Epidemiology and Pathogenesis

Deschler et al in his studies in 2006 found the age-adjusted incidence of AML around 3.4 cases per 100,000 persons. AML can occur in patients of any age, but in general studies have shown that the overall incidence and the proportion of acute myeloid leukemias increase with age.

When childhood AML is considered, Gurney et al in his studies found maximum incidence occurs in the first year of life, and then decreases until age 4, and there after relatively remains constant until adult age group when it again starts to increase.

Approximately 70% of acute leukemias in adults are AML, with a marked increase in incidence in the elderly. The increase is due to AML with MDS-related changes in marrow, which is more common with age, while the in the case of incidence of de novo AML, it remains almost same.

Indian & MMTR Data

As per Madras metropolitian cancer registry, incidence of acute leukemia is rising trend (2, 3). In 1984-88 it constituted 4.0% of total cancer patients. But in 2008 -2010 data, its incidence is increasing and now constitutes almost 6.9% of all cancer burdens (3). Acute myeloid leukemia constitutes the major burden of leukemia in patients with age more than 15 years.

Risk Factors for AML

- **Congenital diseases**

Down syndrome, Severe congenital Neutropenia, Dyskeratosis Congenita, Fanconi anemia

- **Environmental Exposures-**

Ionizing radiation, Benzene exposure, Cigarette smoking

- **Chemotherapy**

Topoisomerase II Inhibitors, Alkylating chemotherapy, Anthracyclines , Anti-tubulin agents

- **Denovo AML**

Classification of AML (WHO 2008) (4)

- **Acute myeloid leukemia with Genetic abnormalities**

  AML with t (8; 21) (q22;q22); RUNX1

  AML with inv (16) CBFB-MYH11

  APL with t (15; 17); PML-RARA

  AML with t (9; 11); MLLT3-MLL

- **Acute myeloid leukemia with Myelodysplasia-related changes**
- **Therapy-related myeloid neoplasm**
- **Acute myeloid leukemia, not otherwise Specified**

Risk stratification of AML (5)

Acute Myeloid leukemia is presently risk stratified on basis of cytogenetic and molecular Abnormality and response to induction therapy.

Good Risk	Intermediate Risk	Poor Risk
CEBP2A double mutated	Normal karyotype+ FLT3-,NPM1 -	Monosomy 7
Core binding factor(CBF) gene Associated AML t (8:21) translocation inversion 16	Numerical Abberation -Y +8 +11 +13	Complex abnormality (>-3 chromosomal abnormalty)
Normal karyoype with FLT3- , NPM1 +	t (9:11),trisomy 8	t(9:22)
t (15 :17),PML RARA+	Del 7q Del 9q	Any Karyotype with FLT3 ITD +ve

Treatment approach for acute myeloid leukemia

Fit patients (< 60-65 years, select patients up to age 75 y) are candidates of intensive therapy. Treatment includes induction therapy and Consolidation therapy. High risk-patients are evaluated for stem cell transplantation at first remission.

Less fit patients (60-75 years and older, or younger patients with significant comorbidities) receive low-intensity therapy. (1)

Treatment recommendations for fit AML patients < 60y or for select patients ≤ 75y (good performance status, minimal co morbidities)

1. Induction therapy:

Combination of cytarabine and anthracycline is recommended [5, 6, 7, 8,]

Cytarabine 100-200 mg/m^2 continuous IV infusion for 7d plus

Daunorubicin 60-90 mg/m^2/day for 3d

Follow-up bone marrow to assess remission is typically done 21-28d after completion of induction chemotherapy

2. Post remission therapy (consolidation) ([9, 10,11,12, 13, 14, 15, 16, 17, 18, 19,20])

All patients should be assessed for risk of relapse. Specific drug regimens are recommended based on a patient's risk of relapse.

Good-Risk patients:

High-dose cytarabine 3 g/m^2 IV over 3h every 12h on days 1, 3, and 5 for 3 cycles or

Intermediate dose cytarabine 1.5gm/m2 over 3 hrs every 12 h on Day 1, 3, and 5 for 3 cycles

Intermediate-risk patients:

High-dose/ Intermediate dose Ara C (1.5gm/3.0 g/m^2 IV) for 3 cycles or Allogeneic bone marrow transplantation

High-risk patients:

Allogeneic stem cell transplantation or

Clinical trial or

High-dose/intermediate dose cytarabine (1.5gm/3.0 g/m) IV over 3h every 12h on days 1, 3, and 5

Acute ProMyelocytic leukemia (APML) is disease with different biology, treated differently with a separate protocol.

REVIEW OF LITERATURE

Hematopoietic growth factors & its role in the treatment of acute myeloid leukemia

The treatment outcomes in AML have significantly improved in the last 2 decades with large number of patients achieving long term disease free survival. One of the major factors contributing to improvement in survival in these patients is improvement in supportive care during therapy.

Over the last 2-3 decades, though little has changed in terms of the chemotherapeutic drugs used in induction and consolidation therapy, notable improvements in intensive care, antibiotic use, growth factor support and antifungal use have all contributed to improvements

Growth factors are usually given to AML patients following completion of chemotherapy, with the goal of attenuating hematologic toxicity. They might help to reduce the duration of neutropenic period and the depth of neutropenia, thus helping to decrease the incidence of febrile infective episodes the duration of hospital stay and cost. This beneficial effect decrease incidence of febrile infective episodes, the duration of hospital stay and cost.

Studies have shown G CSF to have major impact on attenuating morbidity of AML patients undergoing chemotherapy, but have not shown to improve survival. (21, 22)

Growth Factors After Induction Therapy

The Published literature shows mixed results with respect to the benefits of use of growth factors during the remission-induction therapy of AML.

These trials differ from each other with respect to a number of factors like choice of growth factor, patient age and comorbidities, stage of disease and dchemotherapy regimen, including agents and doses used.

A randomized trial was done by Ohno et al (21) done on G CSF administration following AML chemotherapy. Patients with relapsed or refractory leukemia were the study group. They were randomized to receive Growth factors at a daily dose of 200 µg/m or placebo, beginning after completion of Etoposide,mitoxantrone,cyarabine chemotherapy, until absolute neutrophil counts reached 1.5 x 109/L.

Neutrophil recovery was seen to be more rapid in 48 patients who received G-CSF than in 50 patients who did not; which was statistically significant. Median days to neutrophil recovery of 1.0 x 109/L neutrophils was 22 days v 34 days in corresponding groups (P = .0002).

Toxicity was almost similar in both groups, with fever being predominant complication. Infective episodes were significantly less in patients who received G-CSF (P = .028) & the Complete remission rates were 50% in GCSF v 36% in placebo group.This difference was not statistically significant. The incidence of early relapse, sustain remission & survival was not different in both groups which were major concern at that time.

In study by Buchner et al (22) treated 25 newly diagnosed elderly AML patients > 65 years of age, as well as in early relapse, with G-CSF administered b after completion of Daunorubicin, cytarabine, 6 Thio guanine or high-dose cytarabine (HIDAC) and mitoxantrone chemotherapy.

He also found Neutrophil recovery was earlier in patients who received the G CSF after either chemotherapy regimen, compared to historical group (P = .009 and .043 for the two groups,). Differences in median time to neutrophil recovery were 6 and 9 days for the two regimens respectively.

Further results showed Mortality was lower in GCSF arm (14% vs 39%). Complete remission rates were also more in GCSF arm (50% vs 32%) (P =.09), and there was no increased relapse in growth factor arm with equal duration remission. (22, 23)

Rowe et al from Eastern Cooperative Oncology Group (ECOG) reported role of GCSF (24) in 124 newly diagnosed elderly AML patients (Age >65 years) who received cytarabine 100 mg/m2 by continuous infusion and daunorubicin 60 mg/m2 daily for 3 days. They randomized patients to receive G-CSF 250 µg/d or placebo.

Results showed that G-CSF had a statistically significant, favorable effect on neutrophil recovery of 0.5 x 10 9/L , ie ANC >500 (11 days v 14 days , P = .01) and 1.0 x10 9/L neutrophils, ie ANC >1000(12 days v 18 days, P = .001), It also reduced the incidence of infectious toxicity compared to observational arm. (24% on the G-CSF arm v 32% on the placebo, P =.019).

The Complete remission rates were 61% for patients treated in the growth factor arm and 46% for those who received placebo. Median survival was 325 days v 135 days in corresponding groups (P = .035) which was statistically significant. The higher incidence of toxic death in placebo arm was the major cause of decreased survival in these patients.

One of the negative studies on role of growth factors was the Cancer and Leukemia Group B (CALGB) study (25). It had 388 new patients of AML>60 years age ,and were randomized to receive G-CSF or placebo after induction treatment, which had Ara c 200 mg/m2 for 7

days and daunorubicin 45 mg/m2 for 3 days. GCSF was continued until neutrophil recovery of 1.0 x 109/L .

Results showed no significant difference in duration of neutropenia observed between the two groups (16 days v 17 days for placebo). No differences were noted in rates of infectious complication or remission status also.

The ECOG trial and CALGB studies have contradictory results even after large number patients. The main reason was both have used separate regimen. The higher anthracycline dose in the ECOG study would have resulted in a longer duration of neutropenia compared to the CALGB regimen which was milder. This longer neutropenia would have been alleviated by G-CSF in ECOG study. Studies have now clearly shown that dose of Anthracycline is important in determining outcome of AML patients. (22)

Roswell Park Institute conducted a pilot study to determine whether G-CSF could attenuate the hematologic toxicity associated with intensive HDAC and anthracycline induction chemotherapy. (26) GCSF was administered to all patient at dose of 250mcg/day and was continued until the absolute neutrophil count rose to ANC >5000 on 2 consecutive days.

Results showed remission rate with a single course of induction therapy was 75% and 10% induction mortality. Remission had occurred in 86% of patients < 60 years and 65% of those >= 60 years of age. G CSF helped in faster neutrophil recovey. Mortality rate was similar in the two age groups (9% and 10%). So it was concluded that GCSF administered in induction hasten neutophil recovery and decreases complication.

Results of Various studies on G CSF in AML induction

Study	Population	Phase	Outcome	Comments
Ohio et al	Elderly (>65yrs) RCT	Induction	Faster ANC Recovery(22v34)	No risk of increased relapse .
Buschner et al	Elderly/ Relapse AML	Induction	Faster ANC recovery (8v11days)	No risk of inceased relapse
ECOG	Elderly AML RCT	induction	Faster ANC recovery (11v14days)	Decreased mortality in GCSF
CALGB	Elderly (>65y) RCT	induction	Equal days of recovery. No added benefit of GCSF	Negative study
Roswell Park Cancer institute	All Age groups (pilot study)	Induction	Faster ANC recovery	No increased risk of relapse

Controversies of GCSF in AML Induction (27)

There has been great concern that growth factors given to AML patients to promote the growth of residual leukemic cells and thereby increasing the rate of induction failure or early relapse.

Although data are still limited, studies published to date support the conclusion that G-CSF administered to AML patients after induction chemotherapy, with effective cytoreduction, do not increase the risk of remission induction failure due to persistent leukemia, rapid re growth of leukemia cells, or relapse rate.

So at present GCSF administration during AML induction chemotherapy is still a topic of debate, but it is used widely in elderly patients and unfit patients undergoing AML induction to attenuate toxicities.

Guidelines on use of Growth Factor use in cancer

ESMO recommends primary prophylaxis with growth factors for a chemotherapy with a risk of febrile neutropenia >20%.Therapy of Acute leukemia & stem cell transplantation lead to higher risk of febrile neutropenia & potentially lethal complications; so it recommends both G CSF and peg GCSF in these situations(28).

NCCN also recommends prophylactic growth factors for chemotherapy with risk of febrile neutropenia>20% &chance of lethal complications (29).

Evolution of Consolidation Chemotherapy in AML (30, 31 ,32)

According to L1210 leukemia model, Post induction marrow leukemic blasts has 3 log reduction. Further consolidation chemotherapy has shown to bring down blasts to undetectable state. So consolidation chemotherapy is considered standard in acute leukemia. In AML consolidation is given by high dose Cytarabine based chemotherapy.

There is substantial evidence to demonstrate that intensive consolidation therapy in AML patients who achieve complete remission improves remission duration and helps the patients to achieve long-term, disease-free survival. Therapeutic approaches include high-dose or intermediate dose cytarabine chemotherapy. (30, 31)

Evolution of modern Consolidation chemotherapy with Single agent high dose cytarabine arabinoside in AML has mainly been based on the Cancer and Leukemia Group B (CALGB) 8525 trial, which included patients of all age group. All received standard induction with 3 +7 chemotherapy .They were randomly allocated at remission to four cycles of cytarabine at various doses (100 mg/m2 , 400 mg/m2 & 3 gm/m2 given on days 1, 3, and 5).

At the end of analysis it was seen that patients who were allocated to the high-dose ara-C arm experienced a superior EFS & OS (overall survival) compared with those allocated to lower doses of ara-C.This was significant for age <60 yrs of patients (30).

Subgroup analysis of this work demonstrated that the benefit of high-dose cytarabine was mainly in those patients with so-called favorable chromosomal abnormalities at diagnosis ie Core binding factor leukemias (inv 16 and t (8; 21)).

Other conclusion was, this is a toxic and expensive regimen with a low but appreciable rate of treatment-related mortality. To prevent the toxic death supportive care in the form of growth factor became the practice. Second, even among the most good risk arm only about two thirds are cured; patients with high risk disease biology are rarely cured. There have been several efforts to improve on high-dose ara-C post remission therapy in form of adding autologous transplant but was not found fruitful.

On trying to improve outcome further, German Study Alliance Leukemia (SAL group) studied on patients post induction receiving consolidation with either high dose ara c for 3 cycles or multi agent consolidation with mitoxantrone/Amsacrine added to Ara C. According to final analysis, the multi agent consolidation did not prove benefit with regard to disease-free or overall survival.

Recently completed M RC AML15 Trial which studied patients with acute myeloid leukemia has compared 3.0gm/m2 dose of cytarabine

and 1.5gm/m2 of cytarabine used in AML consolidation & has found to have equivalent outcome. (32)

So three cycles of Intermediate / high dose cytarabine chemotherapy has become standard approach in Acute Myeloid Leukemia patients post induction as consolidation chemotherapy.

Growth Factors After Consolidation Therapy

Problems with strategy of single agent cytarabine arabinoside consolidation protocol treatment is that patient have severe myelosupression for approximately 3 weeks post treatment and there is high chance of significant morbidity and mortality during this time. Various Attempts has been done to attenuate this issue. It includes lowering the dose of cytarabine, starting on Growth factors, and early initiation on Antibiotics, improved blood products transfusion etc. Out of which addition of G CSF has made a major impact on outcome of these patients.

Several randomized trials have analyzed whether Growth factors can reduce the duration of neutropenia in AML patients during consolidation phase without compromising the clinical outcome. (33) and they showed that the use of GCSF significantly shortened the duration of neutropenia, which also reduced the need for hospitalization and antibiotic use. (30-31)

Published data from a large randomized, placebo- controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia.(33) The results has confirmed on the safety and efficacy of G CSF in reducing the morbidity associated with AML treatment. It showed that it hastened neutrophil recovery and after a median follow up of 7 yrs there was no difference in DFS/OS and no increased risk of relapse.

In an Eastern Cooperative Oncology Group (ECOG) study reported by Rowe et al (24) of 124 newly diagnosed AML patients ,who was in post induction remission, Growth factor or placebo was administered following consolidation, which consisted of a single course of high-dose cytarabine (1.5 g/m2) .

G-CSF had a significant, favorable effect on neutrophil recovery of 0.5 x 10 9/L (11 days vs 14 days P = .01) and 1.0 x10 9/L neutrophils (12 days v 18 days,P = .001).There was well less incidence of infectious toxicity in GCS arm (24% v 32% in placebo ; P =.019).There was no major difference in incidence of relapse in both groups on long term follow up.

In another phase 3 study of G CSF in consolidation patient of AML (International AML study group) there was statistically significant

decrease in morbidity,febrile complications, incidence of neutropenia, and early neutrophil recovery in GCSF subsets (34). The toxicity profile was also not increased in GCSF subsets nor was relapse rate.

Lowenberg et al in his study evaluated the Quality of Life and effects of GCSF patients for remission induction and consolidation phase of AML therapy. It has also shown to decrease median duration of neutropenia with preserved good quality of life and favourable toxicity profile. No difference was seen in overall survival of these subsets. (35)

There are two studies with use of recombinant growth factors in AML patients during induction & consolidation and have even demonstrated an increase in complete remission (CR) rate and Overall Survival (36,37,38). These are the only studies which have shown overall survival benefit with use of growth factors. But others did not confirm these results.

Various studies on Role of G CSF in AML Consolidation

Study	**Phase**	**Outcome**	**Comments**
Heil et al	Consolidation RCT	Faster ANC recovery + less infection	Decreased mobidity.No increased relapse

Lowenberg et al	Consolidation RCT	Faster ANC recovery	Improved QOL in GCSF. No change in mortality
Rowe et al ECOG	Consolidation RCT	Faster ANC recovery + less infection	Decreased morbidity & sustained remission.
International AML study group	Consolidation	Faster ANC recovery + less infection	Favourable toxicity profile + no increase relapse

In Conclusion use of G CSF is safe and now routine on all AML patients undergoing Post remission Consolidation chemotherapy. It has definitely shown to reduce the duration of severe neutropenia, fastens the neutrophil recovery, decrease febrile complications and thereby decreasing morbidity in these subsets. The impact of these in overall survival of patients in AML requires further studies.

Other uses of GCSF proposed in AML patients

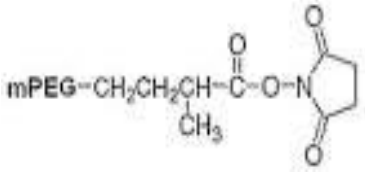
There have been studies on priming of leukemic cells with growth factors in AML, before the start of chemotherapy for more effective cell

kill, but it has not produced satisfactory results and cannot be recommended at present as standard of care.(39)

Growth Factors have been also now routinely used in Mobilization of stem cells during harvest for Donor of AML patient undergoing Bone marrow Transplant. (40)

Pegylated G CSF

Peg filgrastim is a recent introduction to the family of growth factors. It is a 38,000 Da, Pegylated variant of recombinant human granulocyte colony-stimulating factor (G-CSF). Since G CSF is produced in E. coli cells, the molecule is non-glycosylated and therefore, differs from G-CSF isolated from a human cell. Pegfilgrastim is made by attaching a polyethylene glycol (PEG) to filgrastim.(40)

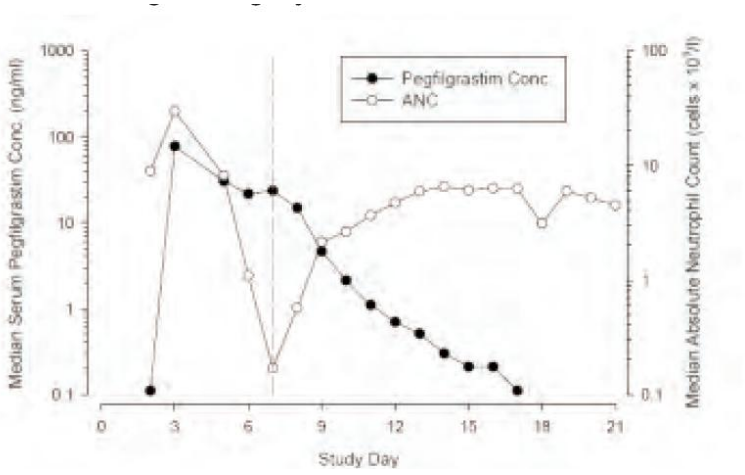


Conventional GCSF **PEG GCSF**

Pharmacokinetics

Single dose of pegylated growth factor when injected subcutaneously,the peak serum concentration occurs upto 16-120 hours ,and studies have found it is maintained during the whole course of neutropenia after myelosupressive chemotherapy. (41)

The elimination of peg filgrastim is not linear with respect to dose, serum clearance decrease with increasing dose. The major advantage of pegylated filgrastim is its neutrophil mediated clearance. Serum level of peg gcsf has been shown to decline rapidly after onset of neutrophil recovery. (42)



Dose

Standard Adult dose >40kg, is 6.0mg subcutaneous-single dose

Studies in children has used dose 100mcg/kg s/c –single dose

Side effect profile

Trials done have showed it is safe in patients, and toxicity is comparable to conventional GCSF.

Most common side effect seen with pegylated GCSF is

1. Bone pains
2. Myalgia
3. Fatigue.

Mainly calf, thigh and lower back are most common sites of pain. Studies have shown up to 40-50% of patients having grade1 of these side effects. But severe toxicities are very rare.

Studies in children has reported mild headache. Some patients also had increased incidence of pedal edema.

Other less common side effects include Flu like illness, Pain at injection site, Anaphylaxis or hyper sensitivity reactions.

Rarely reported cases of Acute respiratory distress syndrome (ARDS) and capillary leak syndrome.

Very rarely fatal splenic rupture has also been reported in patients.

Pegylated growth factors in Cancer Chemotherapy

Various trials have been done about role of Peg GCSF in both solid tumours and lymphoma, to fasten neutrophil recovery and decrease incidence of neutropenia. This has shown to decrease morbidity.

Regimens with an overall risk of febrile neutropenia of ≥20% have been advised to be started on prophylactic Growth factors. These include regimens that are used for treatment of Breast cancer like TAC, CHOP-like regimens used for Non-Hodgkin's lymphoma and the DCF/TPF regimen used for head &neck and gastric cancers etc.

A meta-analysis of five different studies in a total of 600 patients treated for lymphoma or breast cancer showed that a single dose of peg GCSF 6.0mg was significantly more effective than 10–14 days of multiple G CSF in reducing infective episodes (43, 44).

Larger meta-analysis data by Kuderer et al. (45) also suggest that peg GCSF was more effective than GCSF, and that also with a favourable toxicity profile. Analysis found that in patients receiving various chemotherapy regimens (total of 15,763 cycles), the risk of hospitalisation was approximately 30% lower with peg GCSF support than with daily G-CSF (45).

These datas clearly shown that, Pegylated GCSF has shown its non inferiority,ease of administration and favourable toxicity profile compared to conventional G CSF in patients with cancer undergoing various chemotherapy

Pegylated growth factors in pediatric population

Data on role of Peg GCSF safety and efficacy in children at present are scanty but upcoming.

Cesaro et al has studied role of single dose of 100 mcg/kg peg G CSF in mobilizing peripheral blood stem cells (PBSCs) in pediatric patients undergoing autologous stem cell transplant.The results on 36 children showed it to be equally efficacious with favourable toxicity profile (47).

Peg filgrastim was studied for chemotherapy associated neutropenia in children with solid tumors. Median age was 6 yrs (1-20 yrs).They concluded that Peg GCSF following chemotherapy for solid tumors is feasible in children. The duration of neutropenia, incidence of febrile neutropenia, were similar to GCSF historic data. It did not have any added toxicity (48).

Pegylated growth factors AML Consolidation

Acute Myeloid leukemia patients are most of time neutropenic before start of chemotherapy. Before starting consolidation chemotherapy also they are at times infected or would have recovered from major induction chemotherapy. More over further consolidation chemotherapy will worsen neutropenia and thereby resulting in high attendant risk of infection and death.

Growth factors have shown to decrease morbidity in these patients. Pegylated growth factors are now being studied in this setting and its efficacy is compared with conventional GCSF.

But at present there are only very limited available literatures in both Western & Indian studies.

The application of pegylation technology has created a second generation molecule, pegfilgrastim, with significantly altered pharmacokinetic properties. The pegylation markedly reduces renal clearance, leaving neutrophil-mediated clearance as the major route of elimination.(42) As a result, clearance of pegfilgrastim is decreased and serum concentrations are sustained throughout the duration of neutropenia.

A single dose of pegfilgrastim was compared with daily filgrastim for supporting neutrophil recovery in patients treated for low-to-intermediate risk acute myeloid leukemia: results from a randomized, double-blind, phase 2 trials. (49) To minimize inter-patient variability, they excluded high risk cytogenetic patients from study.

Recovery occurred after a median of 17.0 days for pegfilgrastim versus 16.5 days for filgrastim Therapeutic peg filgrastim serum concentrations were maintained throughout neutropenia. Pegfilgrastim was well tolerated, with an adverse event profile similar to that of filgrastim. (49) There was also decrease in hospital stay in Peg filgrastim group of patients.

Compared with 1 pegfilgrastim injection, a median of 16 filgrastim injections were required in induction and 13 in consolidation to ensure ANC recovery. (49)These results showed comparable or similar efficacy of peg GCSF in neutrophil recovery.

The German Cooperative group for AML used Dose-dense induction & further consolidation with sequential high-dose cytarabine and mitoxantone (S-HAM) and pegfilgrastim in AML (50).peg GCSF was given to all patients who was in morphological remission after

induction. Measurable pegfilgrastim plasma levels were observed up to day 14.

Pegfilgrastim clearance was significantly correlated with neutrophil recovery. Median time to neutrophil recovery was 12.7 days after injection.Due to this there was less neutropenia / toxicity and so deaths were also significantly reduced. (50)

In Another phase 2 Trial by Bossi & colleagues did multi centre randomized control trial comparing time of Neutrophil recovery, safety and efficacy of pegylated GCSF compared to conventional GCSF in patients undergoing AML induction & consolidation chemotherapy. (51) The results showed single agent peg GCSF had similar median time to recovery of ANC>500 compared to conventional GCSF. There was no difference in duration of severe neutropenia in both groups. Peg GCSF had a favourable toxicity profile and easy administration .Serum levels of pegylated growth factors were also maintained throughout period of neutropenia. (51)

Various studies on role of Peg GCSF in AML

Study	Phase	Type	Outcome	Comments
Sierra et al (N= 84)	Induction+ consolidation	RCT (peg vs GCSF)	Equivalent ANC (17 vs 16.5)	Safety, no survival benefit
German AML group	Induction + consolidation	RCT	Equivalent effects	Reduced toxic deaths
Bossi et al (N= 84)	Induction+ consolidation	RCT	Equivalent results	Favourable toxicity of peg GCSF.
Kunivayalil etal (N=24)	Consolidation	Comparative (Indian study)	Faster ANC recovery & decreased hospital stay with Peg GCSF	Favourable toxicity profile & equal febrile neutropenia

Peg GCSF in AML Consolidation –Indian Data

Very sparse literature evidence is available from Indian scenario also for use of peg GCSF in AML consolidation.

A comparative study of 30 patients was done in Bangalore, of single-dose pegfilgrastim versus daily filgrastim in patients with acute myeloid leukemia consolidation. (52) In this study median time to

neutrophil recovery was 14 days for pegfilgrastim arm and 17 days for filgrastim arm. In the pegfilgrastim arm 12 (60%) episodes of febrile neutropenia occurred compared to 11 (55%) in filgrastim arm. The median duration of hospitalization was 15 days in pegfilgrastim arm and 18 days in filgrastim arm. Safety profile and complete remission status did not differ between the two groups. (52)

Need of Study:

Incidence of Acute leukemia is rising. AML patients are majority elderly. Major cause of mortality and morbidity has been infections .Peg GCSF has been found to have impact on available very limited literature. In a resource poor country like india even a single day decrease in neutropenia and hospital admission will have major impact on financial burden. Data on role of peg GCSF in AML patients are lacking in both western and Indian studies. Availability of generic versions of peg-GCSF has considerably reduced the cost of therapy with peg GCSF.

MATERIALS & METHODS

Study Design

Prospective Observational non interventional study

Study Period

April 2012- December 2013

Study population

All Acute myeloid leukemia patients (Adult & Pediatric) Undergoing Consolidation chemotherapy in Cancer institute (WIA),Adyar,Chennai

Aim

- To assess efficacy of Peg G CSF in Neutrophil recovery in patients of AML consolidation.
- To compare efficacy of Peg GCSF patients with conventional GCSF subsets

(Historical data from 2011-2012 from patients who had undergone AML consolidation treatment with conventional GCSF)

Primary end point

- Median duration of Neutrophil recovery in patients receiving Peg GCSF in AML consolidation.

Secondary end points

- Incidence of Febrile Neutropenia during consolidation and usage of Antibiotics.
- Side effects & Toxicity profile of peg GCSF in AML consolidation.
- Median Duration of Hospital stay

Materials & Methods

Inclusion criteria

1. All Adults & pediatric patients of AML undergoing consolidation chemotherapy with high /intermediate dose cytarabine.
2. Bone marrow should be in remission before starting consolidation.
3. Patients should provide informed consent.

Exclusion criteria

1. Acute Promyelocytic Leukemia (APML) .
2. Previous history of anaphylaxis to growth factors will be excluded.
3. Combination of any other cytotoxic drug with Cytarabine if used in consolidation will be excluded from study.
4. Any dose of cytarabine other than 3.0gm/m2 or 1.5gm/m2 will be excluded from study.

METHODS

All patients receive total 6 doses of cytosine arabinoside (1.5gm/3.0gm) on alternate day ,twice a day schedule .Peg GCSF will be given exactly 24 hrs after last dose of consolidation. Dose is 100mcg/kg for children & if weight >40kg standard dose of 6.0mg will be given.Route is sub cutaneous. Daily Haemogram will be done from next day of peg GCSF administration. Manual differential count was done and absolute Neutrophil count (ANC) will be calculated. Median day of neutrophil recovery was calculated.

The following parameters were prospectively collected from the patient records:

1. Median day of neutrophil recovery. Day 1 of ANC > 1000 for 3 consecutive days was considered as the day of neutrophil recovery. Time to recovery was taken as 1 day for patients whose ANC remained >500 & didn't have a dip in counts.
2. Day 1 of Platelet count of >50,000 for 3 consecutive days was taken as platelet recovery.
3. Incidence of febrile neutropenia, & its duration
4. Duration of hospital stay

5. Organisms grown and antibiotic /antifungal used.
6. Side effects and toxicity pofile of pegylated GCSF will be carefully assessed and will be graded as per NCI-CTCAEcriteria for all patients with Age >10 years (children <10 yr peg GCSF toxicity not assessed because same scale is not useful)
7. Requirement of Blood (Packed Red cells) and blood Product (single donor/Random Donor) Platelet requirement during consolidation chemotherapy will be noted.

The data from these patients and its variables will be compared with the historical data of patients between April 2011-12 , who received conventional G-CSF.

Statistical Analysis

Descriptive statistics were used for demographic details of the prospective and retrospective cohorts. Time based end points will be described as median values and compared between cohorts using the unpaired t test. Categorical variables will be assessed using the Fisher exact test. Statistical analysis will be done by SPSS software.

Calculation of ANC

$$\text{Absolute Neutrophil Count} = \frac{(\%\ \text{Neutrophils} + \%\text{Bands}) \times \text{WBC}}{100}$$

The unit of ANC is cells per micro liter of blood. Normal ANC is >1500 cells/microliter.An ANC <500 increases the risk of infections.Grading of ANC is done as per NCI recommendation (Refer Appendix 2)

Febrile Neutropenia

Febrile neutropenia (FN) was defined as a single oral temperature >38.3°C (101 F) or two consecutive readings of >38.0°C (100 F) for 1 hour and an absolute neutrophil count $<0.5 \times 10^9$/l, or expected to fall below 0.5×10^9/l.

Duration of febrile neutropenia was counted from 1st day of temperature >100 F until first 2 consecutive days with temperature <38 degree.

Blood Culture sensitivity were sent from both central & peripheral lines (5 ml each) at 1st spike of fever before stating Antibiotics and each time when escalation of antibiotics was planned.

Antibiotic Policy in Febrile Neutropenia

Prophylactic antibiotic is not used as per our institution policy in AMl consolidation.

First-line antibiotics was Cefoperazone + Sulbactum with Amikacin. 2nd line and third-line antibiotic used were Piperacillin+Tazobactum and carbapenem (Meropenem/Imipinem) respectively.

Teicoplanin was added for any patient with suspected/ proven gram positive infection or hypotension or mucositis. Antifungal use will be Amphotericin B/ Voriconazole as per clinical suspicion & further escalated if needed to Caspofungin.

Adverse effect profile & Toxicity Grading of Peg GCSF

Classification & Grading according to NCI-CTCAE (National Cancer institute-Common Toxicity Criteria (Kindly Refer Appendix 3)

Blood/ Blood Product Tranfusion as per institution protocol during AML consolidation.

PRBC transfusion is given if Hemoglobin <7.0gm/dl, symptom due to Anemia, or acute Blood loss.

Platelet transfusion is given for asymptomatic Thrombocytopenia with platelet count <20,000 or any signs of active bleeding manifestation irrespective of platelet count.

RESULTS

Patient Characteristics

A total of 40 patients underwent consolidation therapy during this period. Altogether 116 Number of cycles of consolidation chemotherapy was administered. The baseline characteristics of the patients is given in table no.1&2

Table No.1

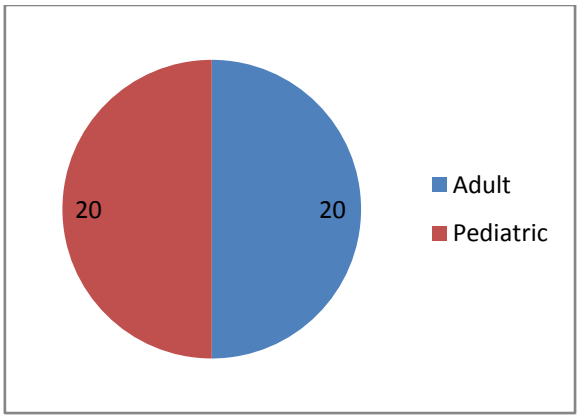
Variable	N
Total No. of patients studied	40
Total No. of cycles consolidation studied	116

Table No.2 **Base line characteristics**

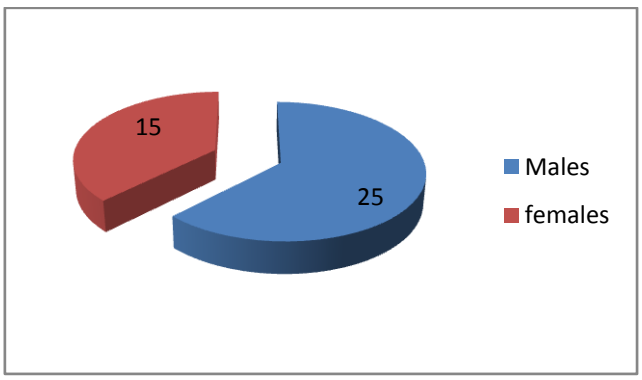
Variable	**N**
Age	
<15 yrs	20
>/=15 yrs	20
Median Age	22 yrs (Range 1-56 yrs)
Gender	
Male	25
Females	15

Risk Category	
Good Risk	19
Intermediate Risk	12
Poor Risk	04
Unknown status	05
Induction received	
3 +7	38/40
ADE	2/40

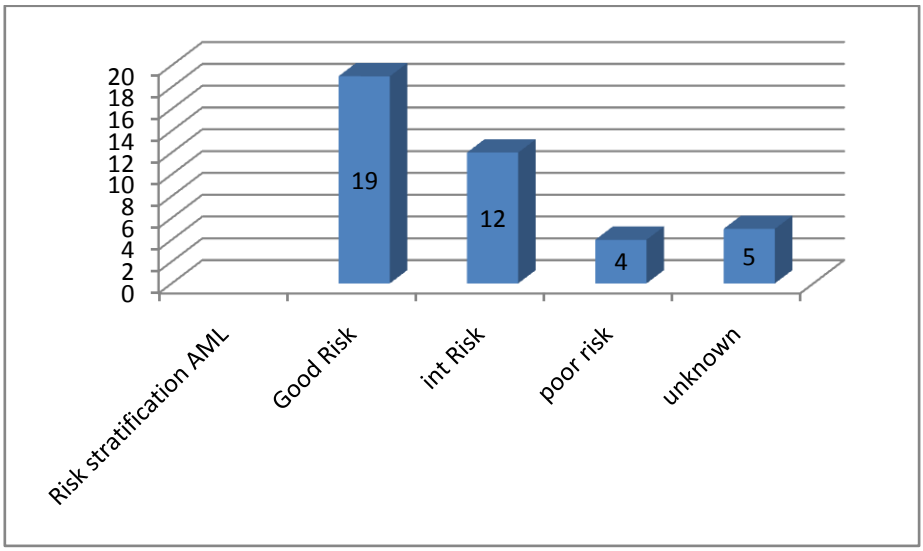
Age Distribution (Fig 1)



Gender Distribution (Fig 2)



Risk Stratification (Fig 3)



t (8:21) was the most common Good Risk cytogenetics seen in about 13 patients. Inversion 16 was seen in remaining 6 patients.

Normal cytogenetics was seen in 11/12 patients with 1 patient having trisomy 8.

All Poor risk cytogenetics was having complex abnormalty (>-3 chromosome abnormalty).

4 patients in the study had no metaphysis available for karyotyping (Due to leucopenia/leukocytosis) and were stratified as unknown prognostic risk stratification group.

FLT3- ITD mutation status & NPM 1 was done in 19 patients.

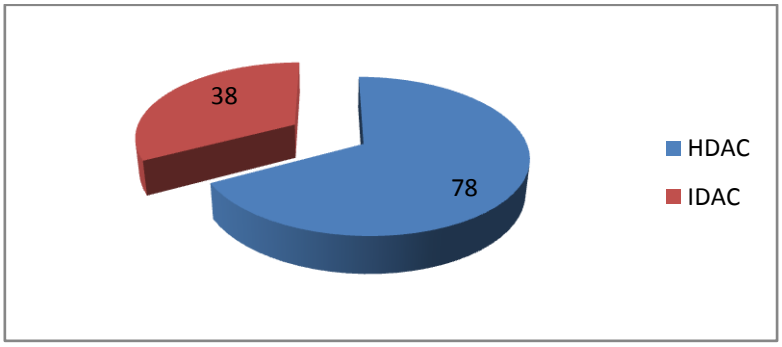
Among these study patients most of them received induction with 3+7 protocol. Only 2 patients received ADE induction.

Consolidation strategy among these total 116 cycles of chemotherapy is as described below.78 cycles was given HDAC(3.0gm/m2) and 38 cycle received IDAC(1.5gm/m2).

Table No.3

Consolidation received	
HDAC (3.0gm/m2)	78 cycle
IDAC (1.5gm/m2)	38 cycle

(Fig 4)



Out of 116 cycles of consolidation therapy, peg GCSF was used in 108 and conventional G CSF was used in 8. This was due to physician preference in 8 of these cycles.

Primary End point

The outcomes with respect to time variables are shown in table below.

Table No.4

Median Duration of Neutrophil Recovery	16.0 days	Range (12-22 days)
Duration of recovery in HDAC	16.4 days	Range (12-22 days)
Duration of recovery in IDAC	16.0 days	Range (12-21 days)

Secondary End Points

Table No.5

Average Duration of Grade 4 Neutropenia	5.8 days	Range (1-11 days)
Median Duration of platelet recovery	19.0 days	Range (14-24 days)
Median Duration of Hospital stay	20.0 days	Range (14-27 days)

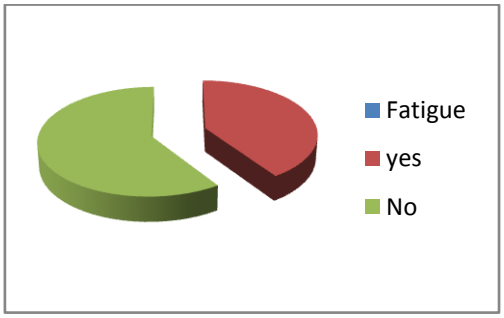
In study the mean nadir WBC count was 300/cumm and mean nadir platelet count was 16,000/cumm .

Toxicity Profile of Peg GCSF

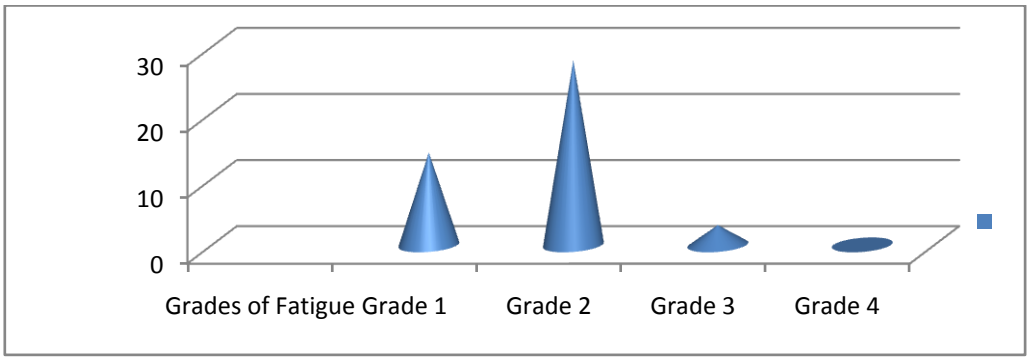
In these study 32/40 patients were assessed for toxicity profile(8 patients were excluded as their age was <10 yrs). Total 92 cycles of pegylated GCSF was studied. Most common side effect noted in study was myalgia/Bone pains and fatigue.

1. Fatigue

Fatigue was experienced in 41 cycles (42%),but majority(38/41 cycles) was mild grade1/2 fatigue. Only 3 cycles had grade 3 fatigue and no grade 4 fatigue was seen. Presence of Fatigue was more common by 3rd cycle of consolidation. (Out of 41 cycles having fatigue 25 was in 3rd cycle of consolidation)

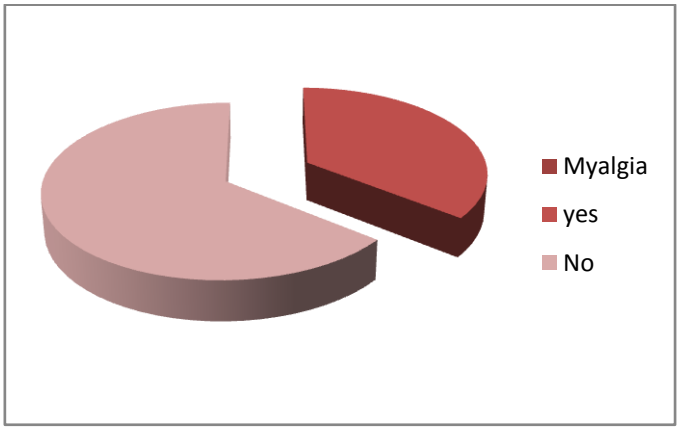


Grades of Fatigue

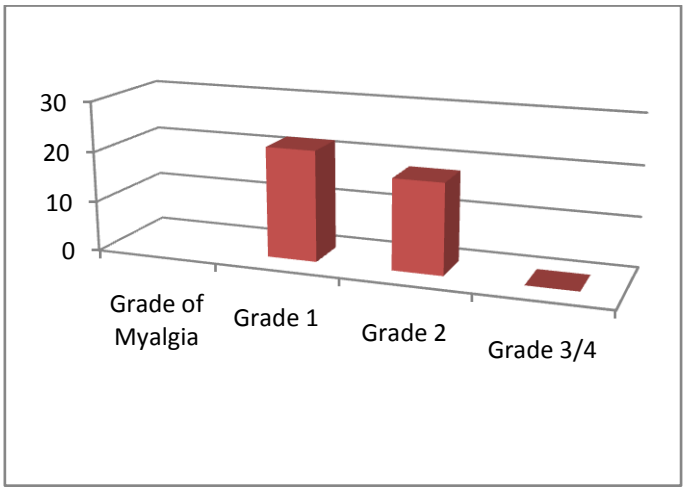


2. Myalgia

Myalgia/Bone pain was reported in 36/92 cycle (38%). All were grade1/2. They were felt mainly in lower back, hip & calf muscle. There was no difference in distribution of myalgia as per cycle of consolidation. There were no reported Grade3/4 bone pains/myalgia in any age group.



Grade of Myalgia



Further details of toxicity in study group are given in detail in below table

Table No.6 **Toxicity details in study Group**

Variable	Present	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	41/92 (44%)	23 (56%)	15 (36%)	3	0
Myalgia	36/92 (39%)	22 (66.1%)	14 (38.8%)	0	0
Bleeding	4 cycles	-	-	-	-
Cellulitis	4 cycles	-	-	-	-
Others	3	-	-	-	-

Out of 4 bleeding – 1 was p/v bleed, 1 was gum bleed and other 2 cases were Epistaxis. There was no life threatening bleeding manifestation in study group.

4 cycles in study population had cellulitis , 2 in psoas muscle and 2 in thigh muscle. Blood C&S grew E.coli. It responded to Antibiotics. Other side effects include 1 pediatric patient in 3rd cycle consolidation complaining of vague head ache, and 2 Adult patients found to have Grade 1 B/L Pitting pedal edema.

No patient developed anaphylaxis,flu-like syndrome, rash or hypersensitivity reactions.

Blood Product Requirement in Consolidation

Table No.7

Median PRBC requirement/cycle	1.0/cycle	Range (1-5/cycle)
Median platelet requirement/cycle	6.0 RDP/cycle	Range (2-15/cycle)

Febrile Neutropenia & Infective Complications Study Group

Table No.8

Total incidence of F N	102 cycles (88.8%)
Incidence of FN in HDAC	89.5%
Incidence of FN in IDAC	88.0%
Most common days infective episodes	Day 10-13

Focus of Infection was found in 29 Patients (28.8%) and here are as follows

- Pneumonia- 16 patients
- Peri Anal region- 12 patients
- Cellulitis – 4 patients
- Colitis - 1 patients

Blood Culture Positivity in AML Consolidation

Blood C& S Positivity in patients in study group- 17 cycles (17.9%) and the most common organism isolated are

Staphylococcal Aureus-total 8 /16 patients. (MSSA- 7; MRSA–1)

Gram Negative Bacilli -4 patients

E.coli/ Acineto bacter-3 patient

Burkholderia species -2 patients

Escalation to 3rd line Antibiotics-

Escalation to 3rd line Antibiotics during course of febrile neutopenia was done in 57 patients (55.5%).

No invasive Fungal/ Viral infection noted.

No Therapeutic Anti fungal/ Anti Viral used in study group.

Mortality

1 Mortality in study group-

48 yr female, Good Risk AML on 3rd HDAC consolidation developed febrile neutropenia. She developed B/L pneumonia +Gram negative septicemia & shock . She had progressive worsening of her respiratory status and expired on Day +18 AML consolidation.

Pediatric Sub group Analysis in Study population (Age <15 yrs)

Table No.9

Variable	Number	
Total Pediatric patients	20	
Sex	Males-13 Females-07	
Median Age group	11 yrs (1-15 yrs)	
Cycles of consolidation studied HDAC IDAC	60 49 11	
Conventional plain GCSF used	1 cycle	
Dose of Pegylated GCSF used	100mcg/ Kg	
Median Duration of Neutrophil Recovery	16.0 days	Range (12-22 days)
Median Duration of Platelet Recovery	19.0 days	Range (14-27 days)
Median Duration of Gr.4 Neutropenia	6.0 days	Range (2-11 days)
Median duration Hospital stay	20 days	Range (16-26 days)

Febrile Neutropenia Incidence & Details in Pediatric Patients

51/60 cycle had fever (86.6%). Escalation to 3rd line Antibiotics was done in 32 cycles (63.4 %). Focus of fever seen in 13 patients

Blood Culture & Sensitivity

13/51cycles had central line culture Positivity (25.2%).

Most common Organism - MSSA (4 patients)

E.coli/ Acinetobacter

Burkholderia (2 patients)

No Rash/Anaphylaxis or injection site pain noted in pediatric patients.

No mortality seen in pediatric age group patients.

Historical Data on Plain GCSF in AML Consolidation (2011-12)

Table 10

Total No. of patients studied	29
No. of cycles Analyzed	50
Median Age	19 yrs (1-58yrs)
Sex	Males 21 Females 8
Consolidation Chemotherapy	HDAC (3.0gm/m2)-39 IDAC (1.5gm/m2)-11
Average GCSF used/ cycle	12.0 Injections
Median Duration Neutrophil Recovery	17.0 days Range (3-22 days)
Median Duration of Platelet recovery	19.0 days Range (16-24 days)
Median Duration of Gr4 Neutropenia	7.0 days Range (2-12 days)
Median Hospital stay/ cycle	21.0 days Range (16-26 days)
Blood Product requirement	PRBC - 1.4/ cycle RDP - 4.0/cycle
Febrile Neutropenia	44/50 cycles (88%)
Escalation to 3rd line Antibiotics	32/45 cycles (71.2%)

Comparison Data on Pegylated Gcsf Patient Subset with Historical Plain Gcsf Subset Study Population.

Table 11

Variable	Pegylated GCSF	Conventional GCSF
Median Day of Neutrophil Recovery	16.0days	17.0 days
Day of Platelet Recovery	19.2 days	19.1 days
Duration of Gr.4 Neutropenia	5.8 days	7.2 days
Hospital Stay	20 days	21.3 days
Febrile Neutropenia	88.8%	88.0%
Escalation to 3rd line Antibiotics	45/78 (55.5%)	27/39 (71.1%)
Blood Product Requirement	PRBC 1.0 /cycle	PRBC 1.2/cycle
	RDP 5.6/cycle	RDP 4.0/cycle
No. of injections	1	~12 inj/cycle
Mortality	1	3

Duration of neutrophil recovery & platelet recovery remained same in both subsets. There was reduction in duration of Grade 4 neutropenia & hospital stay.Blood products were equal, except more platelet requirement in peg GCSF arm.The statistical significance of this comparitive findings were tested.

Statistical Analysis of Data on Patients Receiving High Dose Arac (3.0gm/m2) in Peg-Gcsf & Historical Plain Gcsf Subsets.

(Total no. of cycles of HDAC – N= 78 in peg GCSF & N= 39 in Plain GCSF)

Student t test Analysis

Table No. 12

Variable	**Peg GCSF Mean +- SD**	**G CSF Mean +- SD**	**t**	**P value**
Day of Neutrophil recovery	16.3/2.9	17.7/4.4	-1.593	0.076 (NS) Student t
Duration of Grade4 Neutropenia	5.8/2.4	7.0/3.4	-2.90	0.003 (S) Student t
Duration of platelet recovery	19.3/3.4	19.7/4.0	-.481	0.63 (NS) Student t
Platelet Transfusion	6.0/ 3.6	5.0/2.6	.219	0.82 (NS) Student t
Duration Hospital stay	19.5/3.2	21.0/4.0	-2.33	0.009 (S) Student t

Chi Square Analysis

Table No.13

Variable	**Peg GCSF (N)**	**G CSF (N)**	**Results**
Escalation to 3rd line Antibiotics	45/78	27/39	0.165 (NS) Ficher exact t test
Mortality	1/40	2/29	0.257 (NS) Fischer exact t test

DISCUSSION

There are only very few western & Indian literature available on role of pegylated GCSF in AML patients. This prospective Observational study was done to evaluate their role in neutrophil recovery in AML Consolidation chemotherapy. It also evaluated the toxicity/side effect profile of Peg GCSF and compared the present data with historical data of patients treated in previous year (2011-12).

Our study has shown that single dose of pegylated GCSF has a median day neutrophil recovery of 16.0 days and is seen to have equivalent efficacy compared to multiple injections of conventional GCSF. It has shown to decrease the duration of grade 4 neutropenia . It also had reduced need to escalate to higher antibiotics as well as the hospital stay in these patients. It is also found to have a favourable toxicity profile. As per our knowledge this is the first study looking at efficacy of pegylated GCSF in children in AML consolidation. It was found to be equally effective in them.

The Median Age in study population was 22 years, (Range 1-56 yrs) of patients. Males constituted 2/3rd of patient population. Study by sierra et al included patients 18-74 yrs (49).study by Bosi etal also

included patient 18-70 yrs of age group (51). The available Indian literature by Kunivayalil et al included age group 18-60 yrs (52) and also had a male preponderance.

Risk stratification in our study showed 60% patients in good risk, followed by 30% intermediate risk. Only 5% population were poor risk. Study by Heil et al which looked at role of filgrastim, excluded poor risk patients (34). Sierra et al in his study on role of pegylated GCSF included Good or intermediate risk patients only, as it was expected to have delayed neutrophil recovery in High risk AML induction(49).The available Indian literature has not risk stratified patients with cytogenetics.

In our study the less representation of high risk group is because of institute management protocol. Most of the high risk patients and some intermediate risk patients in our institute directly go to Allogenic Bone marrow Transplant after Induction remission without receiving consolidation chemotherapy.

The primary end point in our study was median day of neutrophil recovery.The average day of neutrophil recovery in study group was 16.0 days.This results are almost similar to western studies.

Initial studies on plain GCSF has shown neutrophil recovery by 18.0days in patients on high dose cytarabine(25).The literature on Pegylated GCSF by sierra et al showed 17.0days for neutrophil recovery(34).The consolidation with HAM (High dose Arac +Mitoxantrone) by German cooperative AML group had neutrophil recovery with median day of 13.0days(38).Bossi etal in his study had neutrophil recovery by 17.0days in peg GCSF arm (43). The available Indian literature, study by kunivayalil et al demonstrated neutrophil recovery by 14.0 days in Pegylated GCSF arm(37).

The definition of neutrophil recovery also varied among studies. The initial study by sierra etal and Bosi et al has taken ANC>500 for 2 days as day of neutrophil recovery. But our study as well as study by kunivayalil et al has taken Day1 of ANC>1000 as day of neutrophil recovery.

Majority of our study population received High dose Ara C (3.0gm).When these data were compared to neutrophil recovery with intermittent dose Ara C (1.5gm) patients; there was no major difference in period of recovery. It may be probably due to low number in intermittent dose group and selection of those patients. It requires further larger study to compare these data.

The secondary endpoints included Platelet count recovery, incidence of febrile neutropenia and hospital stay.The median duration of platelet recovery was 19.0 days. The median duration of hospital stay was 20.0days.

Comparing to existing literature, platelet count recovery is around 19 days (26-27) in conventional GCSF patients in AML consolidation. The existing literature has not studied platelet recovery endpoints in peg GCSF group. Various historical studies differ in taking threshhold of platelet recovery. Some use cutoff of 20,000 with no bleeding manifestation as recovery (especially post Bone marrow transplant), others use threshold of >50,000count. We have used the latter as definition of recovery in our study. This is of significance as thrombocytopenia is also common after administering peg GCSF.

The median duration of hospital stay was 19.0 days in study by sierra etal, and study from Bangalore, Kunivayalil etal had median hospital stay of 15 days in peg GCSF group. In our study patients were discharged by average 20.0 days from hospital.

Febrile neutropenia, incidence & Antibiotic use were studied extensively in our study. There was reported 88% incidence of fever. Study by sierra et al, 77% in peg gcsf arm developed febile neutropenia

during consolidation. Median duration of fever was 2 days; compared to 4 days in our study. Bosi etal also had 80% incidence of febrile neutropenia. The study by kunivayalil et al had 60% incidence of fever.

Toxicity profile of patients with Peg GCSF was studied and graded as per NCI CTCAE criteria version 4.1. Most common side effect noted in study was fatigue and is seen in approximately 41% patients. But majority was grade 1or 2 &only 3% had grade 3 fatigue. Myalgia/Bone pains were seen in 38% patients. All were grade 1/2 and there were no grade 3/4 of these toxicties. There was no significant bleeding abnormality in our study group. Other toxicities were only rarely reported.

Sierra et al in his study had 26% adverse events in peg GCSF subgroup patients. Fatigue was seen in 11% in his study population (But exact grading of fatigue is not done). Bosi etal had 18% fatigue in their study population. Bone pains / myalgia were seen in 7% of patients in study by sierra et al. Study of Peg GCSF in solid tumours had bone pains about 30% patients (42). Most common sites of pain in these studies were also back, lower limb calf and thigh muscles. The available Indian study also had favourable toxicity profile with peg GCSF. No patient had Anaphylaxis reaction or severe life threatening toxicities in our

study group. These results were correlating with existing literature on pegylated GCSF in AML patients.

Statistical analysis with historical patients of conventional GCSF shows significant correlation for duration of severe neutropenia & average hospital stay. There was a trend to significance in duration of neutrophil recovery. The western studies had shown that peg GCSF had equivalent results to GCSF in helping neutrophil recovery & duration neutropenia. Available Indian study had shown efficacy of Peg GCSF over conventional growth factors in hastening neutrophil recovery & there by hospital stay. Other variables including febrile neutropenia, blood product requirement, and platelet recovery had no statistical significance which is similar to existing literature.

There was 1mortality in Peg GCSF group in our study. The cause of death was infective with B/L pneumonia with septic shock. Patient did not recover counts and succumbed to illness by Day 18 of third cycle chemotherapy. Earlier study by sierra & Bosi et al also had 1mortality in Peg GCSF study group which was also due to infection. There was no mention on incidence of mortality in previous Indian study on Pegylated GCSF.

Comparison of Available literature & outcome of peg GCSF with present study

Variable	**Sierra et al**	**Bosi et al**	**Kunivayalil et al**	**Present study**
Age	18-74 yrs	18-70 yrs	18-60 yrs	1-56 yrs
Phase of AML studied	Induction+ consolidation	Induction + consolidation	Consolidation	Consolidation
Risk	Good/Intermediate Risk only	Good/ Intermediate Risk only	Not stratified	All Risk group patients.
Avg. Day of neutrophil recovery	17.0days (peg) V 16.5 days	16.0days (peg) V 16.5 days	15.0day (peg) V 18.0 days	16.0day (peg) V 17.0 days
Febrile neutropenia	77%	80%	60%	88%
Duration of hospital stay	19.0days	Not assessed	15.0days	20.0 days
Comments	Single dose Peg GCSF equivalent to GCSF	Single dose Peg GCSF equivalent to GCSF	Single dose Peg GCSF better than GCSF	Single dose Peg GCSF equivalent to GCSF

As per our knowledge this is the first study on role of pegylated GCSF in AML consolidation in pediatric age group. Dose of peg GCSF

used by us was 100mcg/kg, which was same used by other groups in children for neutrophil recovery (45).The median day of neutrophil and platelet recovery was same as adult population. There was more favourable toxicity profile in children. Bone pain/myalgia was commonest toxicity. There was no anaphylaxis/life threatening toxicity in children. These results are comparable to available scanty evidence of role of Peg GCSF in children.

Our study has shown that single dose of pegylated GCSF may be of equivalent efficacy as compared to multiple daily GCSF injection in treating patients of AML consolidation. Duration of severe neutropenia and hospital stay was less in peg gcsf group in our study, which was statistically significant. This will have a major impact on decreasing cost burden especially on resource limited developing countries. Peg GCSF also limits multiple injections to the patients.

CONCLUSION

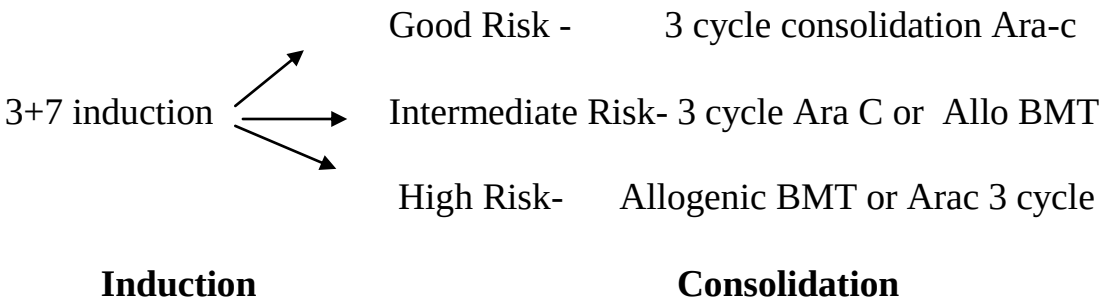
1. Single dose of Pegylated GCSF injection is equivalent to multiple conventional GCSF injections in hastening neutrophil recovery in patients of AML undergoing consolidation chemotherapy.
2. Peg GCSF has shown to decrease the median duration of grade 4 neutropenia, and also lower need for escalation to 3rd line antibiotics in these patients during febrile episode.
3. Peg GCSF has shown to decrease the duration of hospital stay in these patients.
4. Peg GCSF has a favourable toxicity profile with no life threatening side effects.
5. Peg GCSF is well tolerated in pediatric age group also with equal efficacy and tolerable side effect profile.
6. Single dose Peg GCSF limits multiple injections to these patients.

LIMITATIONS OF STUDY

1. Small number of study population, requires larger number for accurate assessment of efficacy.
2. Not a Randomized study, data was compared with historical cohorts.
3. Follow up is short, needs long term follow up.

Appendix 1

Institute AML Management protocol (in Fit patients)



Appendix 2

ANC criteria for grading Neutropenia

NCI Risk Category	ANC
0	Within normal limits
1	≥1500 - <2000/mm³
2	≥1000 - <1500/mm³
3	≥500 - <1000/mm³
4	< 500/mm³

Appendix 3- (NCI -CTCAE Version 4.1)

Adverse effect profile & Toxicity Grading of Peg GCSF

Variable	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	Increased fatigue in relation to the baseline , but without interfering with normal activity	Moderate fatigue Difficulty in carrying out Instrumental activity of daily living. ADL- I	Severe fatigue Difficulty in carrying out self care activity of daily living. ADL-SC	Bed bound or severe disability. LTC
Myalgia	Mild pain without interfering normal activities	Moderate pain Limiting instrumental activity of daily living ADL-I	Severe pain Limiting acitivity of self care ADL-S	Bed bound or severe disability
Vomiting	1-2 episodes in 24 hrs	3-5 episodes in 24 hrs	>6 episodes in 24 hrs or any hospitalization indicated	Life threatening toxicity
Hemoglobin	<10.0 or <LLN	8.0-9.9	6.5-7.9 or Transfusion indicated	Life threatening toxicity

ABBREVIATIONS

AML	-	Acute Myeloid Leukemia
G CSF	-	Growth Colony Stimulating Factors
Peg GCSF	-	Pegylated form of GCSF
DNR	-	Daunorubicin
Ara C	-	Cytarabine Arabinoside
HDAC	-	High Dose Ara C
IDAC	-	Intermittent Dose Ara C
IFI	–	Invasive Fungal Infection
PRC	-	Packed Red cells
RDP	-	Random Donor platelets
SDP	-	Single Donor Platelets
FFP	-	Fresh Frozen Plasma
ANC	-	Absolute Neutrophil Count
ABX	-	Antibioics
RFT	-	Renal Function test
F.N	-	Febrile Neutropenia

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PATIENT INFORMED CONSENT

I _____have been informed by Dr. _____ _____ that I am suffering from blood cancer. The treatment will include chemotherapy which includes the use of anti caner drugs as injections and antibiotics, antifungals, antiviral drugs, as prophylactic and therapeutic purposes. Patient will require central venous line and intensive care monitoring.

These medicines are associated with toxicities, some of which may occur immediately while others can occur at a later date. The common and important immediate side effects of treatment include nausea and vomiting, diarrhea, hair loss, low counts and ulcers in mouth. Patients can have life threatening infection or bleeding complications which can occur during any phase of chemotherapy, but more common during the initial phase of chemotherapy. Rarely patients may develop allergic reaction to drugs causing low BP, sudden cardiac failure and chest discomfort with breathing difficulty during hospitalization. Growth factor support may be needed to improve low counts due to chemotherapy administration. Very rarely the infused drugs may leak through the veins and cause skin ulceration which may require surgical correction. Complications of antibiotics, antifungal drugs and antiviral drugs informed.

Some important late complications like infertility and difficult child bearing and cardiac dysfuncition are potentially possible. Second cancers have also been reported rarely after treatment of primary cancer. I understand that blood transfusion may be required during the course of treatment which may be associated with immediate complications like fever, transfusion reactions and rarely later, liver infection and jaundice.

Response to treatment is variable and depends on the risk stratification of cancer and other related factors pertaining to the disease and the patient. Once there is good response to initial treatment, patient will require further treatment in the form of additional chemotherapy or stem cell transplant. There is chance of cancer coming back at any phase of treatment or during follow up.

After completion of treatment the patient may be required to be followed up regularly. The financial implications of my therapy has been explained to me. The nature of my disease has been explained to me by the doctors, in the language I clearly understand. After understanding all the facts, I am willing for the above mentioned treatment.

WITNESS **DOCTOR** **PATIENT**

PROFORMA

Name : **Sex :** **Age :** **UHID:**

Ward:

Consent obtained : Y/N

Final Diagnosis : AML (Y/N) **Subtype(M1/M2/M3/M4/M5/M6)**

Cytogenetics : Good / Intermediate / poor (Mention -)

Induction : ADE / 3+7 **No.of induction cycles : 1 / 2**

Marrow at end of induction : CR / Not in CR

Date of Starting Consolidation : **PS -**

Date of Administration Peg Gcsf : **Dose Of Peg Gcsf:**

Duration of gr 4 Neutropenia : **Date of Neutrophil recovery :**

Date of Discharge : **Duration Hospital Stay :**

Date of platelet recovery: **Plain GCSF used : (Y/N) (Days/ reason)**

Consolidation Chemotherapy : HIDAC / IDAC / Others

Cycle of consolidation : 1 / 2/ 3 **Dose of Arac : /m2**

Complications in consolidation :

Fever : Y/N **Duration:** **Blood Culture +ve – Y/N (----) Focus-**

Gen. Fatigue : Y/N **Grade:** **1/2/3/4**

Days :

Myalgia : Y/N **Grade:1/2/3/4**

Site :

Bleeding Manifestation : Y/N **Site :**

Cough / pneumonitis :

Abdominal symptoms:

Others :

Antibiotic used : **Cefoperazone / Sulbactum Y/N Days :**

Piperacillin + Tazobactum Y/N Days :

Meropenem/ Imipinem Y/N Days:

Teicoplanin Y/N Days

Amikacin Y/N Days

Antifungal : **Ampho B / Voriconazole / Caspofungin /fluco**

Days –

Antivirals : **Y/N**

Blood products Used : **PRC - RDP - SDP- FFP-**

	Day1	Day7	Day21
RFT			
LFT			
PROTIEN/ALBUMIN			
WEIGHT			
OTHERS			

Haemogram Values: **(From Day of administration of peg GCSF)**

Day											
HB											
TC											
Man DC											
Plt.count											
ANC											

Mortality - Y/N **Day -** **Cause of death –**

Out of study - Y/N **Reason -**